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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,061	PASTAN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 6-8,10-14 and 21-33* is/are pending in the application.

4a) Of the above claim(s) *24-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-8, 10-13 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/1/05; 11/10/05; 3/27/06; 5/3/06.

DETAILED ACTION

1. Then preliminary amendment filed 01 June 2005 has been entered in full.

2. Claims 5, 9, 14-20 and 34-38 are cancelled.

3. Claims 1-4, 6-8, 10-13 and 21-33 are pending.

Election/Restrictions

4. Applicant's election with traverse of the invention of Group I, claims 1-4, 6-8, 10-13 and 21-23 in the reply filed on 12 December 2006 is acknowledged. The traversal is on the grounds that a search of the subject matter of Group I with the subject matter of Group II would not impose an undue burden on the examiner. This is not found persuasive because Applicant has not shown that the groups of inventions have a general inventive concept under PCT rule 13.1. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features, meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. As set forth in the restriction requirement mailed 10/13/2006, Applicants' special technical feature recited in claim 1 is an isolated disulfide Fv protein that specifically binds the epitope bound by monoclonal antibody 8H9 conjugated to a toxin, however, Modak et al in view of Robinson et al and Kreitman et al reads on the claim. Hence, there is no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive concept. Applicant is reminded that search burden is not relevant to unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 24-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

6. Claims 1-4, 6-8, 10-13 and 21-23 are under consideration.

Information Disclosure Statement

7. The information disclosure statement (IDS) filed 01 June 2005, 10 November 2005, 27 March 2006 and 03 May 2006 have been considered by the Examiner. A signed copy of each IDS accompanies this Office Action. It is noted that the references cited on the IDS filed 03 May 2006 duplicate the references cited on of the IDS filed 01 June 2005 and thus, have been crossed out on the IDS filed 03 May 2006 to avoid delays at the time of issue. The references have been fully considered as cited on the IDS filed 01 June 2005.

Specification

8. The examiner acknowledges the abstract submitted in the preliminary amendment filed 01 June 2005, however, the abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

9. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 17, line 8. Applicant's cooperation is requested in reviewing the entire disclosure for additional embedded hyperlinks and/or other form of browser-executable code that require correction. See MPEP § 608.01.

b. The specification at pg. 44, line 26, states "??ORIGINALLY", which appears to be misplaced. Correction and/or clarification is requested.

c. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

10. Claim 10 is objected to as depending from a cancelled claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 6 and 8 are indefinite in the recitation "heavy chain framework region comprising a complementarity determining region..." in claim 6. The knowledge of those skilled in the art is such that each variable region of an antibody comprises four framework regions that flank three complementarity determining regions (i.e., FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4). Thus, it is unclear what is contemplated by a heavy chain framework region that comprises a complementarity determining region. As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

b. Claim 7 is indefinite in the recitation "light chain framework region comprising a complementarity determining region...". The knowledge of those skilled in the art is such that each variable region of an antibody comprises four framework regions that flank three complementarity determining regions (i.e., FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4). Thus, it is unclear what is contemplated by a light chain framework region that comprises a complementarity determining region. As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-4, 6-8, 10-13 and 21-23 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibody 8H9 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Fundamental Immunology, William E. Paul, M.D. ed., 3rd ed. 1993, pg. 242. Therefore, it would require undue experimentation to reproduce the claimed antibody species antibody 8H9.

The specification lacks complete deposit information for the deposit of antibody 8H9. It is unclear whether antibodies possessing the identical

properties of antibody 8H9 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibody.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody 8H9, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of antibody 8H9 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of antibody 8H9 is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the

form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

15. Claims 6-8 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated Fv protein comprising a heavy chain variable region comprising the HCDR1 of residues 31-35 of SEQ ID NO:3, the HCDR2 of residues 50-60 of SEQ ID NO:3 and the HCDR3 of residues 99-107 of SEQ ID NO:3 and a light chain variable region comprising the LCDR1 of residues 157-167 of SEQ ID NO:3, the LCDR2 of residues 183-189 of SEQ ID NO:3 and the LCDR3 of residues 222-230 of SEQ ID NO:3 wherein the Fv protein binds the 8H9 antigen, does not reasonably provide enablement for an isolated Fv protein comprising a heavy chain variable region comprising a complementarity determining region (CDR) that comprises an amino acid sequence of residues 31-35, 50-65 or 99-107 of SEQ ID NO:3 and/or comprising a light chain variable region comprising a CDR that comprises an amino acid sequence of residues 157-167, 183-189 or 222-230 of SEQ ID NO:3 wherein the Fv protein does not bind the 8H9 antigen as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is drawn to engineered antibodies, where the relative skill of those in the art is deemed to be high.

The claims are drawn to a an isolated Fv protein comprising a heavy chain variable region comprising a CDR that comprises an amino acid sequence of

residues 31-35, 50-65 or 99-107 of SEQ ID NO:3 and/or a light chain variable region comprising a CDR that comprises an amino acid sequence of residues 157-167, 183-189 or 222-230 of SEQ ID NO:3. The phrase "comprising a complementarity determining region" reads upon fragments of a variable region and the phrase "comprises an amino acid sequence" reads upon fragments of the recited CDR and variable domain sequences, since a fragment comprising two amino acids of amino acids 99-107 of SEQ ID NO:3, for example, is merely one interpretation of "an amino acid sequence" of residues 99-107 of SEQ ID NO:3. Thus, the claims broadly encompass isolated Fv proteins that do not contain all six CDRs of monoclonal antibody 8H9, three from the heavy chain variable domain and three from the light chain variable domain and do not bind the 8H9 antigen.

The specification discloses only Fv proteins/antibodies comprising all six CDRs from the 8H9 monoclonal antibody (see Examples). The specification does not teach humanized 8H9 Fv proteins that do not contain all six CDRs from the 8H9 monoclonal antibody and wherein the 8H9 Fv proteins bind the 8H9 antigen. There are no working examples of 8H9 Fv proteins that do not contain all six CDRs from the 8H9 monoclonal antibody and wherein the 8H9 fv proteins/antibodies bind the 8H9 antigen. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 1924 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of most antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is

characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, 1982). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an isolated Fv protein, which contains less than the full complement of CDRs from the 8H9 heavy and light chain variable regions in their proper order and in the context of framework sequences which maintain the correct spatial orientation for antigen recognition have the required 8H9 binding function. There is insufficient guidance and direction to assist those skilled in the art in using Fv proteins comprising fragments of the recited CDR sequences (i.e., "an amino acid sequence") of the 8H9 heavy and/or light chain variable regions, or comprising fragments of the 8H9 heavy and light chain variable domains (i.e., "a complementarity determining region"), wherein the Fv proteins/antibodies bind the 8H9 antigen. One of skill in the art could not predictably extrapolate the teachings of the specification limited to 8H9 Fv antibodies that comprise all six CDRs from the 8H9 monoclonal antibody and bind 8H9 to Fv proteins comprising fragments of the recited CDR sequences (i.e., "an amino acid sequence") of the 8H9 heavy and/or light chain variable regions, or comprising fragments of the 8H9 heavy and light chain variable regions (i.e., "a complementarity determining region"), wherein the Fv protein binds 8H9. One of skill in the art would neither expect nor predict the appropriate functioning of the Fv proteins as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul and Rudikoff et al, the lack of guidance and direction in the specification, and the absence of working examples, undue experimentation would be required to practice the claimed Fv proteins that bind the 8H9 antigen with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed Fv proteins and absent working examples providing evidence which is reasonably predictive that the claimed Fv proteins, which contain less than the full complement of CDRs from the 8H9 heavy and light chain variable regions in their proper order and in the context of framework sequences have the requisite 8H9 binding function, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modak et al (Cancer Research, 61:4048-4054, May 15 2001, Ids reference filed 6/1/05) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996).

The claims are drawn to a disulfide stabilized immunotoxin comprising an Fv that binds the same epitope as monoclonal antibody 8H9 or comprising the heavy chain 8H9 CDRs (i.e., residues 31-35, 50-65 and 99-107 of SEQ ID NO:3) and the light chain 8H9 CDRs (i.e., residues 157-167, 183-189 and 222-230 of SEQ ID NO:3) and human heavy and light chain frameworks and a toxin, wherein the toxin is ricin A, abrin, diphtheria toxin, saporin, restrictocin, gelonin or a subunit of Pseudomonas exotoxin (i.e., PE38, PE40, PE38KDEL or PE38REDL). Further, the claims are drawn to a pharmaceutical composition comprising the disulfide stabilized immunotoxin and a pharmaceutically acceptable carrier.

Modak et al tech the hybridoma that produces murine monoclonal antibody 8H9 that recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues (see entire document). Modak et al do not specifically teach a humanized disulfide-stabilized Fv-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising the humanized

disulfide-stabilized Fv-immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Queen et al.

Robinson et al teach Fv derived from a known antibody (see columns 12-22). Robinson et al teach Fv, determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce Fv (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph).

Reiter et al teach disulfide-stabilized immunotoxins (dsFv-immunotoxins) comprising a truncated form of *Pseudomonas* exotoxin (PE38KDEL) that have equal or improved antigen-binding activity compared to their single-chain counterparts, and are easier to produce with high yields and are more stable than single-chain Fv-immunotoxins (scFv-immunotoxins) (see entire document, particularly abstract and pp. 5452, 5457-5458 and Figs. 2, 4-6 and Tables 1-3).

Queen et al teach humanized antigen-binding antibody fragments including single-chain Fvs comprising mouse CDRs and human frameworks that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy as well as pharmaceutical compositions comprising the humanized antigen-binding antibody fragment and a pharmaceutically acceptable carrier, wherein the humanized antigen-binding antibody fragment is preferably as an immunotoxin comprising a toxin such as *Pseudomonas* exotoxin A, ricin, diphtheria toxin, or ricin A chain (see entire document, particularly cols. 10-16, 19-20 and 23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to obtain the nucleic acids encoding the VH and the VL from the 8H9 hybridoma taught by Modak et al and produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) and a pharmaceutical composition

comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a hu8H9 dsFv-immunotoxin and pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Modak et al and Robinson et al and Reiter et al and Queen et al because Modak et al tech the hybridoma that produces murine monoclonal antibody 8H9 that recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Queen et al teach humanized antigen-binding antibody fragments comprising mouse CDRs and human frameworks that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy as well as pharmaceutical compositions comprising the humanized antigen-binding antibody fragment and a pharmaceutically acceptable carrier, wherein the humanized antigen-binding antibody fragment is preferably an immunotoxin. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known 8H9 monoclonal antibody and produce humanized 8H9 dsFv-immunotoxins that are less immunogenic in human tumor patients and are easier to produce with high

yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide humanized 8H9 dsFv-immunotoxins comprising PE38KDEL, ricin, diphtheria toxin, or ricin A chain in a pharmaceutical composition comprising a pharmaceutically acceptable carrier to facilitate administration in human tumor patients as made explicit in the teachings of Queen et al and Reiter et al. Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known 8H9 antibody could be established from the 8H9 hybridoma using techniques disclosed in the reference. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a hu8H9 dsFv-immunotoxin and a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Modak et al and Robinson et al and Reiter et al and Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Cheung [a] (US 2002/0102264 A1, filed 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes

prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Cheung [a] teaches the hybridoma that produces murine monoclonal antibody 8H9 and antigen-binding fragments of the 8H9 monoclonal antibody including single-chain antibody 8H9 (scFv-8H9) linked to a cytotoxic agent as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject (see entire document, particularly pp. 4-6 and Tables 1-4). Cheung [a] does not specifically teach a humanized disulfide-stabilized Fv-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising the humanized disulfide-stabilized Fv-immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Queen et al.

Robinson et al have been described supra.

Reiter et al have been described supra.

Queen et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to

obtain the nucleic acids encoding the VH and the VL from the 8H9 hybridoma taught by Cheung [a] and produce a humanized 8H9 disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a hu8H9 dsFv-PE38KDEL and pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Cheung [a] and Robinson et al and Queen et al and Reiter et al because Cheung [a] teaches the hybridoma that produces murine monoclonal antibody 8H9 and antigen-binding fragments of the 8H9 monoclonal antibody including single-chain antibody 8H9 (scFv-8H9) linked to a cytotoxic agent as well as a pharmaceutical composition comprising the scFv-8H9-cytotoxic agent and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins Queen et al teach humanized antigen-binding antibody fragments comprising mouse CDRs and human frameworks that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known 8H9 monoclonal

antibody and produce humanized 8H9 dsFv-PE38KDEL that are less immunogenic in human tumor patients and are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the humanized 8H9 dsFv-PE38KDEL in a pharmaceutical composition comprising a pharmaceutically acceptable carrier to facilitate administration in human tumor patients. Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known 8H9 antibody could be established from the 8H9 hybridoma using techniques disclosed in the reference. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a hu8H9 dsFv-PE38KDEL and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Cheung [a] and Robinson et al and Reiter et al and Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Cheung [b] (US 2003/0103963 A1, priority to at least 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Cheung [b] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject (see entire document, particularly pp. 5-6 and Tables 1-4). Cheung [b] does not specifically teach a humanized disulfide-stabilized Fv-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising the humanized disulfide-stabilized Fv-immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Queen et al.

Robinson et al have been described supra.

Reiter et al have been described supra.

Queen et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized 8H9 disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized 8H9 disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Cheung [b] and Robinson et al and Reiter et al and Queen et al because Cheung [b] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues and is useful for inhibiting the growth of tumor cells in a subject and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Queen et al teach humanized antigen-binding antibody fragments comprising mouse CDRs and human frameworks that are less immunogenic in human patients compared to mouse antibodies and

thus, better suited for human therapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce humanized 8H9 dsFv-PE38KDEL immunotoxins that are less immunogenic in human tumor patients, are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the humanized 8H9 dsFv-PE38KDEL in a pharmaceutical composition comprising a pharmaceutically acceptable carrier to facilitate administration in human tumor patients in view of the teachings of Cheung [b] and Queen, both teaching antibody compositions comprising a pharmaceutically acceptable carrier for administration. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a humanized 8H9 disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Cheung [b] and Robinson et al and Reiter et al and Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

20. Claims1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Cheung [c] (US 2005/0169932 A1, priority to at least 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a)

might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Cheung [c] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject (see entire document, particularly pp. 5-6 and Tables 1-4). Cheung [c] does not specifically teach a humanized disulfide-stabilized Fv-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising the humanized disulfide-stabilized Fv-immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Queen et al.

Robinson et al have been described supra.

Reiter et al have been described supra.

Queen et al have been described supra

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized 8H9

disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized 8H9 disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Cheung [c] and Robinson et al and Reiter et al and Queen et al because Cheung [c] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues and is useful for inhibiting the growth of tumor cells in a subject and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Queen et al teach humanized antigen-binding antibody fragments comprising mouse CDRs and human frameworks that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce humanized 8H9 dsFv-PE38KDEL immunotoxins that are less immunogenic in

human tumor patients, are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the humanized 8H9 dsFv-PE38KDEL in a pharmaceutical composition comprising a pharmaceutically acceptable carrier to facilitate administration in human tumor patients in view of the teachings of Cheung [c] and Queen, both teaching antibody compositions comprising a pharmaceutically acceptable carrier for administration. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a humanized 8H9 disulfide-stabilized-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of Cheung [c] and Robinson et al and Reiter et al and Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a

nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 1-3, 6-8, 10-13 and 21-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 in view of Reiter et al (Biochemistry, 33:5451-5459, 1994).

The instant claims have been described supra.

Claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 are drawn to a composition comprising monoclonal antibody 8H9 or a derivative thereof and a pharmaceutically acceptable carrier, wherein the antibody is a fusion construct or an isolated antibody comprising the CDRs of monoclonal antibody 8H9 (i.e., recited as SEQ ID Nos:29-34) and human frameworks. Claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 do not specifically teach a humanized disulfide-stabilized Fv-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising the humanized disulfide-stabilized Fv-immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Reiter et al.

Reiter et al have been described supra.

The claims in the instant application are obvious variants of claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a humanized disulfide-stabilized 8H9-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks and a pharmaceutical composition comprising the hu8H9

dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a humanized disulfide-stabilized 8H9-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 and Reiter et al because Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, and are easier to produce with high yields and are more stable than scFv-immunotoxins. Therefore, one of ordinary skill in the art would have been motivated to modify the 8H9 antibody comprising the CDRs of SEQ ID Nos:29-34 and human frameworks as recited in claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 and produce a hu8H9 dsFv-PE38KDEL that is easier to produce with high yields and are more stable than scFv-immunotoxins as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a humanized disulfide-stabilized 8H9-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending Application No. 10/097,558 and Reiter et al.

This is a provisional obviousness-type double patenting rejection.

Claims 1-3, 6-8, 10-13 and 21-23 are directed to an invention not patentably distinct from claims 1-2, 4, 6-7, 9, 11 and 52-54 of commonly assigned copending Application No. 10/097,558. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/097,558, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

23. Claims 1-3, 6-8, 10-13 and 21-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 18-23 of copending Application No. 10/505,658 in view of Reiter et al (Biochemistry, 33:5451-5459, 1994).

The instant claims have been described supra.

Claims 1-11 and 18-23 of copending Application No. 10/505,658 are drawn to a composition comprising monoclonal antibody 8H9 or a derivative thereof and a pharmaceutically acceptable carrier, wherein the antibody is an antibody-fusion construct, including a scFv linked to a cytotoxic agent, or an isolated antibody comprise the CDRs of monoclonal antibody 8H9 and human

frameworks, wherein the antibody is capable of binding the antigen as monoclonal antibody 8H9 or competitively inhibits monoclonal antibody 8H9 and wherein the . Claims 1-11 and 18-23 of copending Application No. 10/505,658 do not specifically teach a humanized disulfide-stabilized Fv-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising the humanized disulfide-stabilized Fv-immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Reiter et al.

Reiter et al have been described supra.

The claims in the instant application are obvious variants of claims 1-11 and 18-23 of copending Application No. 10/505,658 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a humanized disulfide-stabilized 8H9-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a humanized disulfide-stabilized 8H9-PE38KDEL immunotoxin (hu8H9 dsFv-PE38KDEL) comprising the 8H9 CDRs and human frameworks and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of claims 11-11 and 18-23 of copending Application No. 10/505,658 and Reiter et al because Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, and are easier to produce with high yields and are more stable than scFv-immunotoxins. Therefore, one of ordinary skill in the art would have been motivated to modify the 8H9 antibody comprising the 8H9 CDRs and human frameworks as recited in

claims 1-11 and 18-23 of copending Application No. 10/505,658 and produce a hu8H9 dsFv-PE38KDEL that is easier to produce with high yields and are more stable than scFv-immunotoxins as well as a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL immunotoxin and a pharmaceutically acceptable carrier. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a hu8H9 dsFv-PE38KDEL immunotoxin comprising the 8H9 CDRs and human frameworks and a pharmaceutical composition comprising the hu8H9 dsFv-PE38KDEL and a pharmaceutically acceptable carrier for therapeutic benefit in human tumor patients in view of claims 1-11 and 18-23 of copending Application No. 10/505,658 and Reiter et al.

This is a provisional obviousness-type double patenting rejection.

Claims 1-3, 6-8, 10-13 and 21-23 are directed to an invention not patentably distinct from claims 1-11 and 18-23 of commonly assigned copending Application No. 10/505,658. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/505,658, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C.

102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Patent Examiner
Art Unit 1643

DB
February 15, 2007